(51) International Patent Classification 6 : A61K	A2	(11) International Publication Number: **WO 99/45887**
		(43) International Publication Date: 16 September 1999 (16.09.99)

(21) International Application Number: PCT/US99/04508

(22) International Filing Date: 2 March 1999 (02.03.99)

(30) Priority Data:
09/037,096   9 March 1998 (09.03.98)   US

(71) Applicant: TEMPLE UNIVERSITY OF THE COMMON-WEALTH SYSTEM OF HIGHER EDUCATION [US/US]; Broad Street and Montgomery Avenue, Philadelphia, PA 19122 (US).

(72) Inventors: PILLAY, Viness; Cooney Apartments, Apartment 120, 1300 West Cecil B. Moore Avenue, Philadelphia, PA 19122 (US). FASSIHI, Reza; 1223 Cedar Road, Ambler, PA 19002 (US).

(74) Agents: ANDERSEN, Robert, L. et al.; Ratner & Prestia, 301 One Westlakes (Berwyn), P.O. Box 980, Valley Forge, PA 19482–0980 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: MONOLITHIC TABLET FOR CONTROLLED DRUG RELEASE
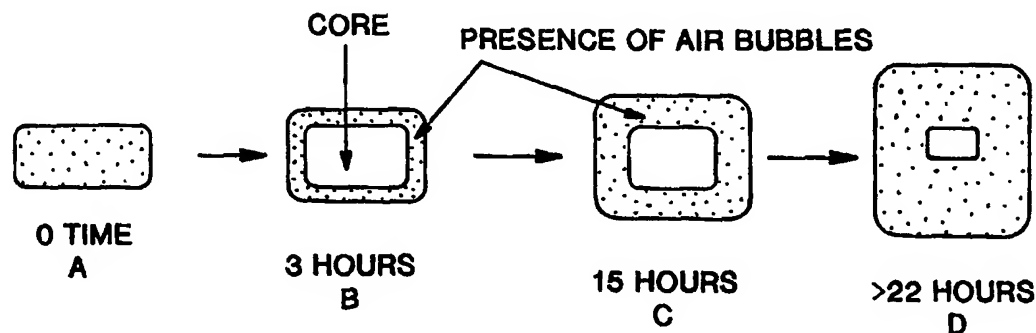
(57) **Abstract**

A swellable hydrophilic matrix tablet that delivers drugs in a controlled manner over a long period of time and is easy to manufacture. More specifically, the drug is disposed in a matrix composed of HPMC or polyethylene oxide, in the presence of a salt, which may be a combination of salts. Suitable salts include sodium bicarbonate, sodium chloride, potassium bicarbonate, calcium chloride, sodium bisulfate, sodium sulfite, and magnesium sulfate. Outward diffusion of the drug is controlled by an inwardly progressing hardening reaction between the salt and the dissolution medium, possibly also involving the drug itself.

- 1 -

MONOLITHIC TABLET FOR CONTROLLED DRUG RELEASE

BACKGROUND OF THE INVENTION

The present invention pertains to a controlled release dosage form, based on a modified hydrophillic matrix composition.

Controlled release pharmaceutical dosage forms have received much attention in recent years and are highly desirable for providing a constant level of pharmaceutical agent to a patient over some extended period of time. The use of single or multiple unit dosage forms as controlled drug delivery devices encompasses a wide range of technologies and includes polymeric as well as nonpolymeric excipients. These dosage forms optimize the drug input rate into the systemic circulation, improve patient compliance, minimize side effects, and maximize drug product efficacy.

The use of controlled release products is frequently necessary for chronic drug administration, such as in the delivery of the calcium-channel blockers nifedipine and diltiazem and the beta-adrenergic blocker Propranolol in the management of angina and hypertension For delivery system design, physiochemical properties and intrinsic characteristics of the drug, such as high or low solubility, limited adsorption, or presystemic metabolism, may impose specific constraints during product development.

Advancements of extended release drug products have come about by the simultaneous convergence of many factors, including the discovery of novel polymers, formulation optimization, better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities, and the introduction of biopharmaceutics in drug product design.

One aspect of research about controlled-release delivery systems involves designing a system which produces steady-state plasma drug levels, which is also referred to as zero-order drug release kinetics. To meet this objective, numerous design variations have been attempted, and their major controlling mechanisms include diffusion/dissolution, chemical reactions, the use of osmotic pump devices, and multiple layer tablet designs, all of which incorporate numerous manufacturing steps and many

associated drug release mechanisms. The complicated processes involved in the manufacture of such ultimately contributes to increased costs to the consumer.

One attractive design for potential zero-order drug release is the use of hydrophilic swellable matrices. Drug diffusion from the matrix is accomplished by swelling, dissolution and/or erosion. The major component of these systems is a hydrophilic polymer. In general, diffusivity is high in polymers containing flexible chains and low in crystalline polymers. With changes in morphological characteristics, the mobility of the polymer segments will change and diffusivity can be controlled. Addition of other components, such as a drug, another polymer, soluble or insoluble fillers, or solvent, can alter the intermolecular forces, free volume, glass transition temperature, and consequently, can alter the transport mechanisms. Cost is also a factor in these modified compositions. Still better controlled, time dependent drug release from these compositions is a continuing objective of research in this area, as is controlled diffusivity compositions which are more easily manufactured. Such compositions, which are more easily manufacturable, have the potential to lower cost of the dosage form.

SUMMARY OF THE INVENTION

The present invention is a new monolithic dosage form that delivers pharmaceutically active agents in a controlled release manner, and that is easy to manufacture. This dosage form, in a form such as a monolithic tablet, may approach zero order delivery of drugs which are either of high or low solubility. This dosage form or tablet is comprised of a hydrophilic swellable matrix, in which is disposed a pharmaceutically active agent and a salt The salt, either in combination with the drug, or another salt upon reaction in an aqueous medium, causes a hardening reaction of the matrix. The rate of outward diffusion is controlled by exposing the product to an aqueous medium. This in turn causes a hardening reaction to occur in a time dependent manner from the outer boundaries towards the inner boundaries of the product; the hardened reaction product, in turn limits outward diffusion of the drug as the inward ingress of aqueous medium causes a progressive hardening from the outer boundaries of the dosage form or tablet in a direction towards the inner core there.

- 3 -

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 1 of the present invention and formulations A1-A5 of Table 1.

Figure 2 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 2 of the present invention and formulations B1-B5 of Table 2.

Figure 3 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 3 of the present invention and formulations C1-C5 of Table 3.

Figure 4 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 4 of the present invention and formulations D1-D5 of Table 4.

Figure 5 is a graph showing the fractional release of diltiazem hydrochloride from the tablets in accordance with Example 5 of the present invention and formulations E1-E5 of Table 5.

Figure 6 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 6 of the present invention and formulations F1-F5 of Table 6.

Figure 7 is a graph showing the fractional release of Propranolol HCl from tablets in accordance with Example 7 of the present invention and formulations G1-G2 of Table 7.

Figure 8 is a graph showing the fractional release of Propranolol from tablets in accordance with Example 8 of the present invention and formulations H1-H2 of Table 8.

Figure 9 is a graph showing the fractional release of Verapamil HCl from tablets in accordance with Example 9 of the present invention and formulations I1-I2 of Table 9.

- 4 -

Figure 10 is a graph showing the fractional release of Verapamil HCl from tablets in accordance with Example 10 of the present invention and formulations J1-J2 of Table 10.

Figure 11 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 11 of the present invention and formulations K1-K2 of Table 11.

Figure 12 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with example 12 of the present invention and formulations L1-L2 of Table 12.

Figure 13 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 13 of the present invention and formulations M1-M4 of Table 13

Figure 14 is a graph showing the fractional release of diltiazem hydrochloride from tablets in accordance with Example 14 of the present invention and formulation N1 of Table 14.

Figure 15 is a graph showing the fractional release of Metoprolol from tablets in accordance with Example 15 of the present invention and formulations O1-O3 of Table 15.

Figure 16 is a graph showing the fractional release of diltiazem hydrochloride from tablets using salt combinations of sodium bisulfate, potassium bicarbonate, magnesium sulfate, and calcium chloride.

Figure 17 is a graph showing the fractional release of formulation A5 of the present invention during exposure to continuously changing pH levels.

Figure 18 is a schematic representation depicting the dissolution of the floatable monolithic matrix tablet over time.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses formulations for the controlled release, preferably zero order release, of bioactive material from a new monolithic system.

- 5 -

These formulations are based on simple swellable hydrodynamically balanced monolithic matrix tablet in which may be incorporated a range of water-soluble (low to high) bioactive drugs and salts. Extended or zero order release is accomplished through the novel application of polymeric matrix modification, as detailed below, by incorporating a salt in a swellable matrix:

As a tablet passes through the human digestive tract, it is subjected to pH values ranging from 1.5 to 7.4. The saliva of the mouth has a neutral pH, the stomach has a pH varying from 2.0-4.0, and the pH of the intestines carries a pH between 5.0-7.5. Therefore, it is important to consider the effects of this pH range on dissolution of a drug tablet. For a drug to approach zero-order release, it's dissolution must be independent of the pH in the surrounding environment.

Through processes of ionic interaction/complexation/molecular and/or self association between a drug and a salt or salt/drug combinations, homogeneously dispersed in a swellable polymer such as hydroxypropylmethylcellulose (HPMC), modify the dynamics of the matrix swelling rate and erosion of the swellable polymer, in accordance with variations in an external pH environment ranging from 1.5-7.0.

These interactions result in controlled matrix hardening. Such hardening is responsible for the control of polymer erosion/dissolution and drug release rates. By design, solvent penetrates the periphery of the tablet and a rapid initial interaction between drug and salt embedded in the polymeric matrix causes immediate hardening of the outer tablet boundary, the rate of hardening consistently decreases toward the center of the matrix core in a time-dependent manner over a long period of time (e.g. 24 hours).

The effervescent nature of sodium bicarbonate causes a generation of gas within the tablet and production of air bubbles. These air bubbles may result in floatation of the tablet, which may increase the gastric residence time of the tablet and result in a prolonged release of the drug in the acidic environment. In addition, this enhances the total mean gastrointestinal residence time and allows for increased biavailability. This is shown schematically in Figure 18, where the tablet progresses over time from an intact and unswollen state to a floatable matrix which is loose and clear.

- 6 -

The differential rate of matrix hardening is the driving principle in the novel system of the present invention, which is dependent on and controlled by the rate of liquid ingress to the tablet core. With the simultaneous time-dependent decrease in gel layer integrity, the rate of drug diffusion decreases. This phenomenon compensates for the increase in diffusion path length and decrease in the surface area of the receding core which arises from the swelling property of the polymer. Hence, better controlled, preferably zero order, drug release is achieved. The drug release process can be tailored for up to 24 hours. Control of the changes in core hardness and synchronization of the rubbery/swelling front and described receding phase boundaries as well as erosion of the dissolution front boundary (i.e. erosion of the tablet periphery) results in controlled drug release, preferably including zero order kinetics. Optionally, polymer matrix hardening is also easily achievable through double salt interaction. This binary salt combination is also uniformly dispersed in the polymeric matrix, which through ionic interaction/complexation/molecular and/or self association, increases the relative strength and rigidity of the matrix, resulting in controlled drug release with a similar mechanism to that described above.

Drugs such as the calcium-channel blockers Diltiazem and Verapamil and the beta-adrenergic blocker Propranolol (as the hydrochloride salts), with water solubilities of 50, 8 and 5% respectively, have been used in the present invention.

One hydrophilic matrix material useful in the present invention is HPMC K4M. This is a nonionic swellable hydrophillic polymer manufactured by "The Dow Chemical Company" under the tradename "Methocel". HPMC K4M is also abbreviated as HPMC K4MP, in which the "P" refers to premium cellulose ether designed for controlled release formulations. The "4" in the abbreviation suggests that the polymer has a nominal viscosity (2% in water) of 4000. The percent of methoxyl and hydroxypropryl groups are 19 - 24 and 7-12, respectively. In its physical form, HPMC K4M is a free-flowing, off-white powder with a particle size limitation of 90% <100 mesh screen. There are other types of HPMC such as K100LVP, K15MP, K100MP, E4MP and E10MP CR with nominal viscosities of 100, 1500, 100000, 4000, and 10000 respectively.

- 7 -

Formulations of the present invention may also include salts such as sodium bisulfate, potassium bicarbonate, magnesium sulfate, calcium chloride, sodium chloride, sodium sulfite and sodium carbonate in their formulations. Fig. 16 illustrates the use of some of these salts with diltiazem hydrochloride.

5   It is believed that an interaction between drug and salt forms a complex in the surrounding swellable matrix in a layered fashion because it occurs in a time-dependent manner as the solvent media for drug release penetrates the tablet inwardly.. Likewise, because the catalyst for the initiation of drug release is liquid ingress, so too is the rate of drug release controlled by the inwardly progressive hardening of the salt

10   complex. .

A binary salt system (e.g. calcium chloride and sodium carbonate) may also be used, may also be used, in which case the hardening reaction may be a function of interaction between the salts. Calcium chloride may be incorporated to form a complex with sodium carbonate. With this combination, the reaction products are insoluble

15   calcium carbonate and soluble channel former, sodium chloride. Hence the calcium carbonate embeds itself in the polymer matrix, initiates hardening and slowly dissolves with liquid ingress and the subsequent creation of diffusion channels as drug diffuses out. In a similar way, other binary salt combinations display time-dependent "hardening/de-hardening" behavior.

20   The amount of salt to be used may easily be determined, by those skilled in the art, taking into consideration the solubility of the drug, the nature of the polymer and the required degree of matrix hardening desired. In case of diltiazem hydrochloride in a HPMC matrix, 100 mg of sodium bicarbonate provides suitable matrix hardening for zero order controlled release, while in the case of the same amount of drug in a different

25   polymer such as polyethylene oxide, 50 mg of sodium bicarbonate appears to be ideal for the attainment of controlled zero order release.

On the basis of the drug release profiles presented in Figure 14, the change in pH of the dissolution media, from acidic to basic, does not markedly change the pattern except for a burst effect at $pH \geq 5.4$, which is not a limiting factor considering the fact

30   that the tablet will not be immediately exposed to pH 5.4 in the gastrointestinal tract, and

- 8 -

instead must first pass through the acidic gastric environment. This has been confirmed by subjecting the formulation (A5) to a carefully synchronized test of continuous changing pH environment simulating the gastrointestinal tract. This has been achieved with the aid of the Bio Dis Release Rate Tester (Vankel Instruments). The resulting drug release profile is provided in Figure 17. The addition of salt in the formulation is not used as a pH modifying agent. Therefore, the relative salt proportion is essentially irrelevant with respect to changes in pH.

EXAMPLES

The formulations of the inventions are illustrated by the following examples. The use of particular polymers, buffers, and inert additive and fillers in the particular amounts shown are not intended to limit the scope of this invention but are exemplary only. All ingredients are initially individually massed and simultaneously incorporated. The premix is blended in a V-blender. The resultant homogeneous powder is compressed into tablets using conventional technologies.

EXAMPLE 1

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	A1 (ctrl)	A2	A3	A4	A5
Diltiazem HCl	100	100	100	100	100
HPMC K4M	200	200	200	200	200
Sodium bicarbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

As shown in Figure 1 the results of this Example reflect a progressive decrease in the release of diltiazem hydrochloride with an increase in the sodium bicarbonate content within the HPMC matrix. This increase in salt content is accompanied by an increase in the linearity of the drug release profiles. In particular, formulation A5, which contains 100mg of sodium bicarbonate provides drug release which most closely approaches zero order over a 24-hour period.

EXAMPLE 2

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	B1 (ctrl)	B2	B3	B4	B5
Diltiazem HCl	100	100	100	100	100
PEO 4M	200	200	200	200	200
Sodium bicarbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

- 10 -

This Example demonstrates, as depicted in Figure 2, that salt induced controlled drug release is also observed with polyethylene oxide as the polymeric matrix. This suggests that the present invention is not polymer-limited. The linearity in profiles seen at even the lowest salt concentration, 10mg. At higher concentrations (above 50mg), the profiles tend to become concave, which suggests that the level of salt required for linear drug release is lower for polyethylene oxide than for HPMC.

EXAMPLE 3

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	C1 (ctrl)	C2	C3	C4	C5
Diltiazem HCl	100	100	100	100	100
HPMC K4M	200	200	200	200	200
Sodium carbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

Example 3 demonstrates and Figure 3 illustrates that the suppression of diltiazem release from HPMC matrices can also be attained by the application of other salts such as sodium carbonate, and linearity of release rate is still observed.

- 11 -

EXAMPLE 4

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	D1 (ctrl)	D2	D3	D4	D5
Diltiazem HCl	100	100	100	100	100
PEO 4M	200	200	200	200	200
Sodium carbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

5   Medium: Potassium chloride buffer pH 1.5

        Volume: 900 ml

        Apparatus: Rotating paddle

        RPM: 50

        Example 4 demonstrates and Figure 4 demonstrates that in using

10   polyethylene oxide as the polymeric matrix, and sodium bicarbonate as the incorporated

        salt, an initial slow release followed by a more rapid linear release can be obtained. The

        initial slow release phase causes dilution of the drug in the gastric environment and

        subsequent reduction in gastrointestinal irritation.

- 12 -

EXAMPLE 5

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	E1 (ctrl)	E2	E3	E4	E5
Diltiazem HCl	100	100	100	100	100
HPMC K4M	200	200	200	200	200
Potassium bicarbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

As depicted in Figure 5, Example 5 demonstrates the use of potassium bicarbonate as the incorporated salt. Linear retardation of drug release is observed after an initial burst phase corresponding to approximately 10% of the drug. This phenomenon has importance in the provision of a mini-loading dose prior to gradual metering of the drug which may be useful in some combinations.

- 13 -

EXAMPLE 6

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)				
	F1 (ctrl)	F2	F3	F4	F5
Diltiazem HCl	100	100	100	100	100
PEO 4M	200	200	200	200	200
Potassium bicarbonate	0	10	50	75	100
TOTAL WEIGHT OF TABLET	300	310	350	375	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

In this example, potassium bicarbonate is incorporated in a polyethylene matrix system. The result are seen graphically in Figure 6. Suppression of drug release achieved while still maintaining a linear drug release. In addition, the suppression of drug release is virtually unchanged at salt concentrations beyond 50mg/tablet.

- 14 -

EXAMPLE 7

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	G1 (ctrl)	G2
Propanolol HCl HPMC K4M Sodium bicarbonate	100 200 0	100 200 100
TOTAL WEIGHT OF TABLET	300	400

DISSOLUTION CONDITIONS

5   Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

This example, as depicted in Figure 7, demonstrates that HPMC and

10   sodium bicarbonate are a suitable combination for the release of drugs such as

propranolol. The presence of sodium bicarbonate results in a substantial suppression of

drug release, as compared to the use of HPMC alone.

- 15 -

EXAMPLE 8

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	H1 (ctrl)	H2
Propanolol HCl	100	100
PEO K4M	200	200
Sodium bicarbonate	0	100
TOTAL WEIGHT OF TABLET	300	400

DISSOLUTION CONDITIONS

5 Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

   As depicted in Figure 8, Example 8 demonstrates the use of potassium
10 bicarbonate as the incorporated salt with polyethylene oxide as the polymeric matrix.
Linear retardation of drug release is observed upon the addition of 100mg of salt.

- 16 -

EXAMPLE 9

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	I1 (ctrl)	I2
Verapamil HCl	100	100
HPMC	200	200
Sodium bicarbonate	0	100
TOTAL WEIGHT OF TABLET	300	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

The use of Verapamil HCl in the present invention is demonstrated in Example 9 and depicted in Figure 9. As shown, the use of 100mg of sodium bicarbonate results in a decreased rate of release of Verapamil HCl from a matrix. The formulations I1-I2 of Table 9 are particularly relevant in this regard.

- 17 -

EXAMPLE 10

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	J1 (ctrl)	J2
Verapamil HCl	100	100
PEO 4M	200	200
Sodium bicarbonate	0	100
TOTAL WEIGHT OF TABLET	300	400

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

Example 10 demonstrates and Figure 10 illustrates that by selection of a suitable polymer for the matrix, a more controlled retardation of Verapamil hydrochloride may be effected. Although the release curve deviates from linearity toward concavity, such a profile is desirable when a slow onset of drug action is preferred. The concavity in release is evident only with polyethylene oxide. This is due to the sensitivity, in this combination, of the drug release profile to low salt content.

- 18 -

(Comparative) EXAMPLE 11

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	K1 (ctrl)	K2
Diltiazem HCl	100	100
HPMC K4M	200	200
Lactose	0	150
TOTAL WEIGHT OF TABLET	300	450

DISSOLUTION CONDITIONS

5   Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

Figure 11 is a graph of data from (Comparative) Example 11, showing the
10   fractional release of diltiazem hydrochloride from hydrophillic matrix tablets in the
absence of salt and with lactose as a salt substitute. The addition of 150mg of lactose, as
compared to the salt addition of other examples, resulted in no significant change in the
release pattern. In this case the high solubility of diltiazem is the dominant factor in
determining release rate.

- 19 -

EXAMPLE 12

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	L1 (ctrl)	L2
Diltiazem HCl	100	100
HPMC K4M	200	200
Sodium bicarbonate	100	100
Lactose	0	150
TOTAL WEIGHT OF TABLET	400	550

DISSOLUTION CONDITIONS

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

In Example 12, as depicted in Figure 12, compositions like those of Comparative Example 11 are modified by the addition of sodium bicarbonate. In each case, the formulations L1-L2 of Table 12 exhibit a more linear drug release rate, as compared to the control sample of Comparative Example 11. This illustrates that the presence of relatively large amounts of excpients such as lactose do not alter the principle of a drug release which is based on differential hardening rate within the matrix and in turn, results in a greater potential in formulation flexibility.

- 20 -

EXAMPLE 13

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)			
	M1 (ctrl)	M2	M3	Dilacor XR® M4*
Diltiazem HCl	240	240	240	240
HPMC K4M	200	200	250	n/a
Sodium bicarbonate	0	100	100	n/a
TOTAL WEIGHT OF TABLET	300	310	350	936

* Commercial multitablet, multilayer preparation

5   DISSOLUTION CONDITIONS:

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

10   Figure 13 is a graph showing the fractional release of diltiazem
hydrochloride from the hydrophillic matrix tablets in accordance with Example 13 of the
present invention and formulations M1-M4 of Table 13. The swellable, floatable
monolithic tablet system, when formulated with a salt such as sodium bicarbonate
(100mg) exhibits a drug release profile which is similar to the commercial multilayer
15   multitablet system of Dilacor® XR. Each commercial capsule of Dilacor® XR contains 4
three-layered tablets equivalent to 240mg of Diltiazem hydrochloride.

- 21 -

EXAMPLE 14

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)
	N1
Diltiazem HCl	100
HPMC K4M	200
Sodium bicarbonate	100
TOTAL WEIGHT OF TABLET	400

DISSOLUTION CONDITIONS

5 Medium: Potassium chloride buffer pH 1.5, Potassium phosphate buffers pH 5.4, 6, 6.4, and 6.8.

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

10   Figure 14 demonstrates the influence of dissolution medium pH on the release of Diltiazem HCl. On exposure of the tablets to an increasingly basic environment, a more pronounced burst effect is observed, while still approaching a zero order drug release. Comparatively, a change in dissolution medium pH does not produce marked variation in drug release when compared to the release at pH 1.5.

- 22 -

EXAMPLE 15

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)		
	O1 (ctrl)	O2	O3
Metoprolol Tartrate	100	100	100
HPMC K4M	200	200	200
Sodium bicarbonate	-	100	200
Calcium chloride	-	100	200
TOTAL WEIGHT OF TABLET	300	500	700

DISSOLUTION CONDITIONS

Medium: Deionized water pH 5.5.

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

Figure 15 illustrates the influence of double salt interaction on the control of the 100% water soluble drug, matoprolol tartrate. As the salt content is increased from 100 to 200mg in both cases, there is a progressive decrease in drug release. This is indicative of an increase in matrix hardening when higher salt contents are used in the formulation, which in turn causes a slower drug release effect.

- 23 -

EXAMPLE 16

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)			
	P1	P2	P3	P4
Diltiazem HCl	100	100	100	100
HPMC K4M	200	200	200	200
Sodium bisulfate	100	0	0	0
Potassium bicarbonate	0	100	0	0
Magnesium chloride	0	0	100	0
Calcium chloride	0	0	0	100
TOTAL WEIGHT OF TABLET	400	400	400	400

DISSOLUTION CONDITIONS:

Medium: Potassium chloride buffer pH 1.5

Volume: 900 ml

Apparatus: Rotating paddle

RPM: 50

Example 16, as depicted in Figure 16, demonstrates that controlled drug release may also be attained by the use of other salts. As a result, the formulation is not be restricted to sodium bicarbonate. The quantity of salt used dictates the degree of drug release suppression which approaches zero-order.

- 24 -

EXAMPLE 17

FORMULATIONS

INGREDIENTS	FORMULATIONS (mg/tablet)	
	Q1 (ctrl)	Q2
Diltiazem HCl	100	100
HPMC K4M	200	200
Sodium bicarbonate	-	100
TOTAL WEIGHT OF TABLET	300	400

DISSOLUTION CONDITIONS

5   Medium: Row 1 - Potassium chloride buffer pH 1.5 (6 vessels)

Row 2 - Potassium chloride buffer pH 3 (6 vessels)

Row 3 - Potassium phosphate buffer pH 5.4 (6 vessels)

Row 4 - Potassium phosphate buffer pH 6 (6 vessels)

Row 5 - Potassium phosphate buffer pH 6.4 (6 vessels)

10   Row 6 - Potassium phosphate buffer pH 6.8 (6 vessels)

Duration spent by tablet in each row:

Row 1 - 4 hours

Row 2 - 0.5 hours

Row 3 - 0.5 hours

15   Row 4 - 6 hours

Row 5 - 6 hours

Row 6 - 7 hours

- 25 -

Total duration of test: 24 hours

Volume of medium in each vessel: 220 ml

Apparatus: Bio Dis Release Rate Tester (Vankel Instruments)

Dips per minute (dpm): 10

Example 17, as depicted in Figure 17, illustrates that by conducting one continuous test using media which simulates the gastrointestinal milieu as well as simulating the gastrointestinal transit time, the drug release from formulation Q2 maintains essentially a controlled zero-order release. This indicates that the formulation is relatively insensitive to changes in gastrointestinal pH.

- 26 -

What is Claimed:

1.   A controlled release drug delivery formulation comprised of a hydrophilic swellable matrix in which is disposed a pharmaceutically active agent and a salt.

2.   A controlled release drug delivery formulation as recited in claim 1 wherein said salt, either alone or in combination with said pharmaceutically active agent, upon reaction in an aqueous medium, forms hardened area within the matrix, said hardened area limiting the outward diffusion of said pharmaceutically active agent.

3.   A controlled release drug delivery formulation as recited in claim 1 wherein said salt is selected from the group consisting of sodium chloride, sodium bicarbonate, potassium bicarbonate, sodium citrate, sodium bisulfate, sodium sulfite, magnesium sulfate, calcium chloride, potassium chloride, and sodium carbonate

4.   A controlled release drug delivery formulation as recited in claim 1 wherein said polymeric matrix is HPMC or polyethylene oxide.

5.   A controlled release drug delivery formulation as recited in claim 1 wherein said pharmaceutically active agent is of high solubility.

6.   A controlled release drug delivery formulation as recited in claim 1 wherein said pharmaceutically active agent is of low solubility.

7.   A controlled release drug delivery formulation as recited in claim 1 wherein said pharmaceutically active agent is diltiazem, propranolol, or verapamil.

8.   A method of controlling the rate of outward diffusion of a pharmaceutical formulation product consisting of forming said product from a composition including a swellable, hydrophillic matrix, a pharmaceutically active agent and a salt, said product having an inner core surrounded by an outer surface, exposing said product to an aqueous medium such that a hardening reaction occurs in a time dependent manner from the outer surface toward said inner core, and said pharmaceutically active agent diffuses outwardly from said inner core toward said outer surface, the rate of said diffusion being limited by said inwardly progressing hardening reaction.

FIG. 1

FIG. 2

FIG. 3

FRACTION RELEASED

FIG. 4

FIG. 5

FRACTION RELEASED

FIG. 6

FRACTION RELEASED

FIG. 7

FRACTION RELEASED

TIME (HOURS)

| · H1 (CTRL)   + H2 |

FIG. 8

FRACTION RELEASED

FIG. 9

FRACTION RELEASED
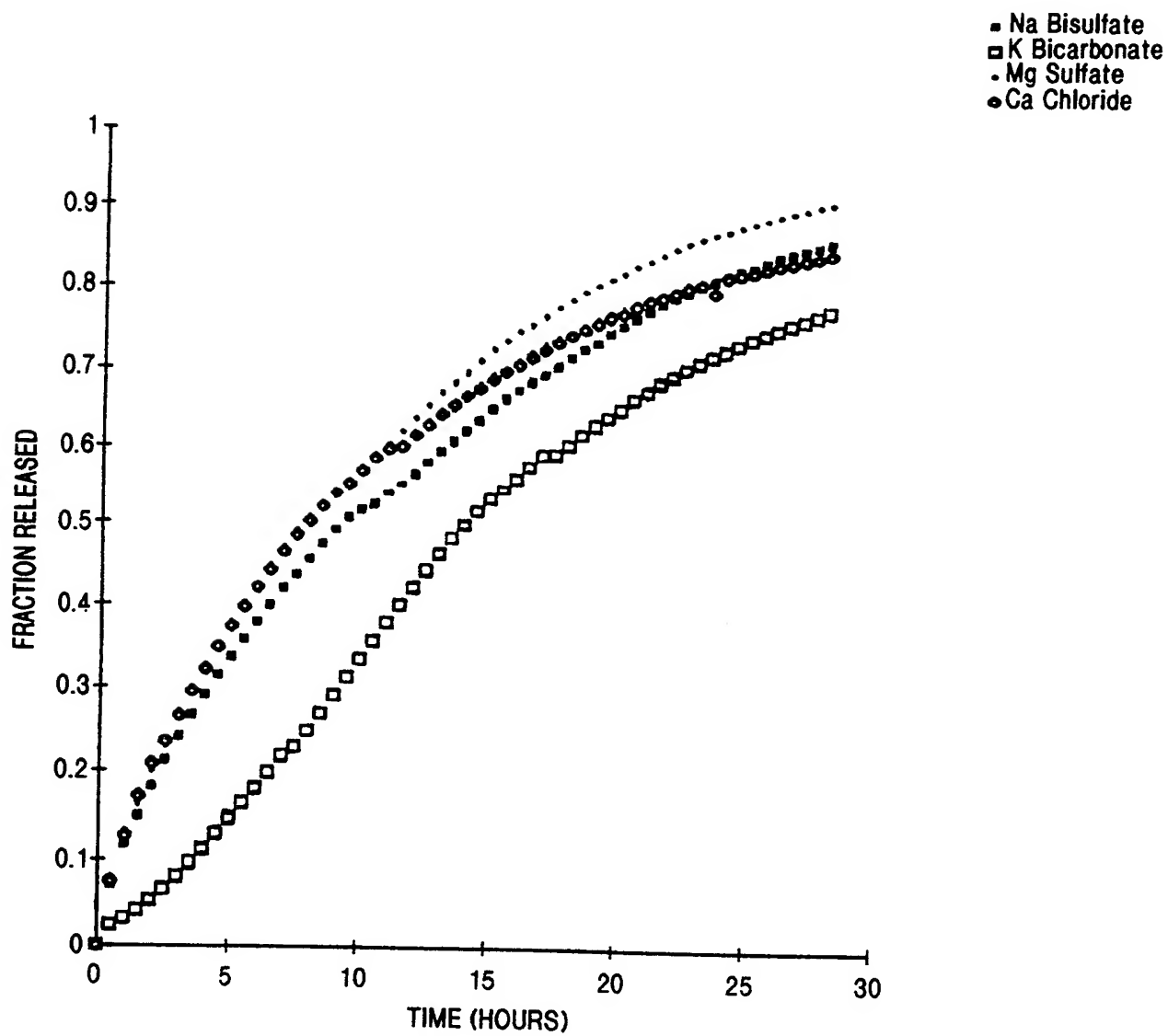

FIG. 10

FIG. 11

FIG. 12

FRACTION RELEASED

FIG. 13

FIG. 14

FRACTION RELEASED

FIG. 15

FIG. 16

FIG. 17

FIG. 18